REMARKS

Reconsideration of this application is requested.

Claims 1 and 28 have been amended to include the features of claims 4 and 5 as alternatives. Claims 4 and 5 have been retained to cover separately the indicated alternatives.

The Examiner will also note that the term "elution" has been added to claims 1 and 28 for purposes of improving clarity. No new matter is involved.

The claims pending for the Examiner's consideration are claims 1-28. All of these claims are thought to be allowable, particularly in view of the amendments made to applicants' claims 1 and 28, it being noted that claims 2-27 all depend, directly or indirectly, from claim 1.

The Examiner is requested to reconsider the Section 102(b) rejection of claims 1, 2, 6-8, 10-14, 16-21, 25 and 28 as anticipated by Berglund et al. (U.S. 6,090,288). While the applicant does not agree with the basis for the Examiner's rejection, the aforementioned amendment of claims 1 and 28 to include the features of claims 4 and 5, should obviate the rejection. It is noted, in this regard, that claims 4 and 5 were not included in the Examiner's Section 102(b) rejection based on Berglund et al. and it is evident that the reference does not disclose the applicant's invention as defined by the amended claims.

The Examiner is also respectfully requested to reconsider the Section 103(a) rejection of claims 3-5 and 24 as unpatentable over Berglund et al., as applied against claim 1, in view of Bambara et al. These references, no matter how considered, do not disclose or suggest the invention represented by applicant's claims 3-5 and 24 or, for that matter, any of the applicant's other claims as presented herein.

As the Examiner has recognized, Berglund does not disclose or suggest the features of applicant's claims 4 and 5, now part of applicant's independent claims 1 and 28. The key part of the Berglund teaching in this regard is the composition of Buffer F. This is formed by the addition of 2M NaCl to Buffer E. Buffer F, therefore, comprises a substantially higher concentration of metal salts than Buffer A (20mM sodium phosphate). Accordingly, the linear pH gradient teaching of Berglund not only employs a pH gradient, but also a substantial increase in the concentration of metal salts in the elution solution. Significantly, at column 13, lines 29 to 50, Berglund compares the performance of Buffer E (relatively low metal salt concentration) with that of Buffer F for elution at pH 9, the same pH as employed in the linear pH gradient of Experiment 7

referred to by the Examiner. At Column 13, lines 45 to 50, the use of Buffer E is taught to produce a fraction containing contaminants. This problem is directly taught to be overcome by the use of the high-salt Buffer F. The clear teaching of Berglund is that the purification of oligonucleotides using an increasing pH gradient also requires a substantial increase in metal salt concentration. This is exactly the opposite to the applicant's invention as brought out in the amendments to claims 1 and 28.

Bambara cannot fill in the clearcut deficiencies of Berglund with respect to the applicant's invention. In this regard, the applicant notes the Examiner's comment regarding applicant's claims 4 and 5 (now a part of claims 1 and 28) that "Bambara et al. teach use of 0.2 M triethylamine bicarbonate buffer at pH 7.5 which is substantially free of metal salts followed by 0.2 M methylamine bicarbonate buffer at pH 8.5 which has no increase in salt concentration" (page 9, lines 12-14 of the Examiner's action). However, there is clearly no basis in Bambara or Berglund to use the Bambara buffer in anything resembling either the Berglund process or the applicant's. Presumably the Examiner's thinking, in rejecting claims 4 and 5 on the combination of Berglund and Bambara, is that the skilled person would contemplate the use of Bambara's triethylamine bicarbonate buffer in the process of Berglund. This thinking can only be based on hindsigsht in the light of the applicant's disclosure. Furthermore, in view of Berglund's clear teaching of the necessity for an increasing salt concentration for the elution of oligonucleotides while using a pH gradient, it is submitted that the skilled person would have absolutely no motivation to contemplate the use of the buffers of Bambara in the method of Berglund. Indeed, Bambara's teaching is to load the oligonucleotide at pH 8.5 using 2M triethylamine bicarbonate buffer, then to reduce the pH to 7.5 using 0.2M triethylamine bicarbonate buffer in order to remove the impurity. Bambara, therefore, teaches the use of a decrease of pH and a decrease of ionic strength in order to separate impurities from oligonucleotides. This approach is diametrically opposed to the approach taught by Berglund. The skilled person would not contemplate combining the buffers of Bambara with those of Berglund. To do so would require the skilled person to completely ignore the key teachings of both Bambara and Berglund. Accordingly, the claims of the present application would not be obvious to one of ordinary skill in the art over the combination of Berglund and Bambara.

For the reasons indicated above, the applicant requests the Examiner to withdraw the Section 103 rejection of claims 3-5 and 24 based on Berglund et al. considered with Bambara et al. It is simply inappropriate to combine these references

as proposed and even if the references are considered together, when there is no reason to do so, the applicant's invention would not result.

The Examiner is requested to reconsider the Section 103(a) rejections of claims 9, 15, 22, 23, 24 and 27 based on Berglund et al. with various secondary references. While the applicant does not agree with the Examiner's position as stated in these rejections, detailed comment thereon is not thought necessary as it is evident on the record that the Examiner's reference combinations do not disclose or suggest the features of claims 4 and 5 which have been added to claim 1.

The application is thought to be in condition for allowance and such action is requested.

Respectfully submitted,
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